## REMARKS

Applicants thank the Office for the attention accorded the present Application in the January 6, 2006, Office Action. In that Action, Claims 1-14 are pending and Claims 1-14 were rejected under 35 USC §103(a) as being unpatentable over Powell et al.(US 6,140,319).

**35 USC §103(a) rejection:**

The Office has rejected Claims 1-14 under 35 USC §103(a) as being unpatentable over Powell et al. The Office states that Powell et al. teach a single dosage unit of a vasopeptidase inhibitor combined with a beta-blocker and an antiplatelet agent where the difference is the inclusion of a vasopeptidase inhibitor. The Office further states that absent a clear indication in the specification or claims of the basic and novel characteristics of the present invention, the transition phrase "consisting essentially of" will be construed as equivalent to "comprising" and that the Applicants have the burden of showing that the introduction of additional steps or components would materially change the characteristics of Applicants' invention.

Applicants respectfully traverse.

Contrary to the Office's assertion, the addition of a vasopeptidase inhibitor would substantially change the characteristics of the present invention. Vasopeptidase inhibitor and omapatrilat, as taught by Powell et al., in combination with a beta-adrenergic blocking agent would result in a dosage unit that inherently has added risk for some individuals with cardiovascular disease.

No agent that is a vasopeptidase inhibitor is presently marketed in the United States and there is no assurance that this category of agent will ever reach the United States market. The vasopeptidase inhibitor omapatrilat cited by Powell et al. was found to have side effects out of proportion to beneficial effects when compared to other agents, especially, a high rate of anaphlactoid reactions, and it failed to meet the standard for United States FDA approval.

In addition, the Declaration of Robert E. Weinstein, M.D. (submitted herewith) indicates that reactions to ACE inhibitors are often overlooked or missed by practitioners. According to Dr. Weinstein, greater than 75% of patients he treated were referred by other physicians. Dr. Weinstein in an expert in his field and has over twenty years of practice in the sub-specialty of allergy and clinical immunology, which focused upon the diagnosis and treatment of respiratory disorders such as asthma, skin disorders such as angiodedema and urticaria, and also drug reactions that manifest as respiratory or skin problems. Dr. Weinstein indicates that when asked by other physicians to consult on patients with a cough thought to be asthma or other respiratory disorder, Dr. Weinstein found the cough was due to an ACE inhibitor that the patient was taking. Further, Dr. Weinstein also found the cause to be an ACE inhibitor when asked to consult on patients having swelling.

Dr. Weinstein's declaration is evidence that warning labels on medications do not render obvious to those of ordinary skill in the art (i.e. physicians) the interactions and side effects of using ACE inhibitors since the referring physicians missed the connection between the medication and their patients' symptoms or misdiagnosed the

cause of the patients' symptoms.

Powell et al. discloses that vasopeptidase inhibitors possess "...in a single molecule both angiotensin converting enzyme (ACE) inhibitory activity and neural endopeptidase (EC24:11; NEP) inhibition activity" and "are also referred to as ...ACE/NEP inhibitors." (Column 1, lines 9-16).

The following scientific literature teaches that, by virtue of its ACE inhibitory properties, the addition of a vasopeptidase inhibitor to the present invention would change the characteristics of the invention in "material," and in some instances, unexpected ways. These include increased cardiac mortality, increased readmission rates, and increased restenosis after coronary stenting with the addition of a vasopeptidase inhibitor. Some of these changes would not be due to effects of the vasopeptidase inhibitor itself, but rather due to interaction with aspirin and/or the beta-blocker components of the present invention. Powell et al. does not anticipate these interactions.

1. *There is increased cardiac morbidity and mortality in patients with coronary artery disease resulting from the interaction of aspirin (claimed in the present invention) combined with an ACE inhibitor.*

In an evaluation of over 4000 hospitalizations for congestive heart failure, Guazzi, et al. found that survival was worse in individuals taking the combination of an angiotensin converting enzyme inhibitor with aspirin compared to without aspirin (Guazzi et al., "Aspirin-angiotensin-converting enzyme inhibitor coadministration and

mortality in patients with heart failure: a dose-related adverse effect of aspirin." Arch Intern Med. 2003 Jul 14;163(13):1574-9). (See the Abstract in Exhibit 01-83006). This study demonstrates a "material" and undesirable effect from combining aspirin, a medication of the present invention, with an ACE inhibitor.

Another study has found that "combining aspirin with ACE inhibitors is associated with higher early readmission rates than use of ACE inhibitors alone..." (Harjai KJ, Nunez E, Turgut, Newman J.. "Effect of combined aspirin and angiotensin-converting enzyme inhibitor therapy versus angiotensin-converting enzyme inhibitor therapy alone on readmission rates in heart failure." Am J Cardiol. 2001 Feb 15;87(4):483-7). (See Exhibit 02-83006). This study similarly demonstrates a "material" effect, early readmission, resulting from the combined dosing of aspirin, a component of the present invention, and an ACE inhibitor.

Another example of worsened outcomes with the combination of aspirin and an ACE inhibitor is found in the study of Nguyen et al. (Nguyen KN, Aursnes I, Kjekshus J., "Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)." Am J Cardiol. 1997 Jan 15;79(2):115-9). (See Exhibit 03-83006). In reexamining a previous study by Swedberg K et al. entitled "Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)" that appeared in the New England Journal of Medicine, 1992 Sep

3;327(10):678-84, the authors found that aspirin was a significant predictor of increased mortality. This effect had been initially overlooked.

2. *There is increased restenosis after stenting resulting from the interaction of aspirin (claimed in the present invention) combined with an ACE inhibitor.*

In a corollary study, Ujiie Y et al. found higher revascularization rates after coronary stenting in individuals receiving the combination of ACE inhibitor and aspirin. "The combinations of an ACEI...with aspirin...are ineffective for the prevention of in-stent restenosis, and an ACEI may even promote intimal proliferation after stent implantation." (Ujiie Y et al. Effects of angiotensin-converting enzyme inhibitors or an angiotensin receptor blocker in combination with aspirin and cilostazol on in-stent restenosis. Int. Heart J. 2006 Mar;47(2):173-84). (See Exhibit 04-83006)

3. *There is increased mortality in patients with coronary artery disease resulting from the interaction with beta blockers (claimed in the present invention), combined with an ACE inhibitor, and an angiotensin-receptor blocker.*

In a randomized trial, Cohn et al. found an adverse effect on mortality and morbidity in individuals receiving the combination of valsartan, an angiotensin-receptor inhibitor, an ACE inhibitor, and a beta-blocker, and raised concern about the safety of these medications in combination. Cohn acknowledged that these findings were unexpected: "An unexpected finding emerged, however, from post hoc analysis of the data on concomitant therapy. Within the...population that was being treated with both

an ACE inhibitor and a beta blocker at base line, there was a significant adverse effect of valsartan on mortality..." (Cohn et al., "A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure." N Engl J Med 2001 Vol 345, 1667-75, see Page 1671, Col 1). (See Exhibit 05-83006). Subsequent clinical study has yielded less threatening data, however, this report underscores the potential for unexpected results from the combining of agents suggested by the Examiner to have "the same utility (treatment of cardiovascular disorders)" and argues against assuming that it is obvious to unconditionally combine agents for therapeutic benefit.

*4. Additionally, there are fetal malformations associated with ACE inhibitors.*

Use of angiotensin-converting-enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is presently contraindicated because of fetal malformations, and the FDA mandates a "black box warning" to this effect on their label. In a very recent study of 29,507 infants, those exposed to ACE inhibitors in the first trimester of pregnancy were also found at increased risk for malformations of the cardiovascular system and the central nervous system. It was concluded that exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided. (Cooper WO, et al., "Major congenital malformations after first-trimester exposure to ACE inhibitors." N Engl J Med. 2006 Jun 8;354(23):2443-51). (See Exhibit 06-83006). This serious, side effect would constitute an additional "material" effect of adding an ACE inhibitor to the present invention, and a reason not to combine such an

agent, that is, so as not to result in inadvertent dosing with an overlooked ACE inhibitor within a combination medication during pregnancy.

The Office responds to Applicants' arguments about the anaphalactoid side effects of vasopeptidase/ACE inhibitors as follows:

> "Applicant argues that the vasopeptidase inhibitor that is taught by Powell et al. in combination with a beta-blocking agent would result in a dosage unit that inherently has added risk... In response one can find side effects and warnings attached to every medicament..."

The Office's statement that warnings are attached to every medicament would suggest a high level of awareness of the anaphalactoid side effects of ACE inhibitors among practitioners. In this instance, however, the medical literature is contrary to this expectation and reflects a surprising and unexpectedly different reality. The titles of the following three articles alone, speak volumes (underlining-- emphasis added) (See Exhibit 07-83006):

> "Oral angioedema secondary to ACE inhibitors, a frequently overlooked association: case report and review." Hurst M, Empson M., N Z Med J. 2006 Apr 21;119(1232):U1930.

> "Angioedema due to angiotensin-converting enzyme inhibition: an association frequently unrecognized." Cicardi M, Conciato L, Agostoni A., Ann Ital Med Int. 1997 Jan-Mar:12(1):8-10.

> "Angiotensin-converting enzyme inhibitor-induced angioedema: still unrecognized." Finley CJ, Silverman MA, Nunez AE., Am J Emerg Med. 1992 Nov;10(6):550-2.

The following medical literature further points out that anaphylactoid reactions

with ACE inhibitors are often missed or misdiagnosed. Additionally, reactions may occur well after the onset of treatment making them more confusing. These reactions may be severe or life-threatening.

> Pavletic A. Late angioedema caused by ACE inhibitors underestimated. Am Fam Physician. 2002 Sep 15;66(6):956, 958. "...late onset angioedema often goes undiagnosed because many physicians are unfamiliar with it...If the diagnosis is missed, recurrent and more severe episodes may occur with potentially serious consequences. Fatal cases have also been described." "Three patients underwent unnecessary laparotomies before the correct diagnosis was made." (See Exhibit 08-83006).

> Gabb GM, Ryan P, Wing LM, Hutchinson KA. Epidemiological study of angioedema and ACE inhibitors. Aust N Z J Med. 1996 Dec;26(6):777-82. "The association of ACE-Is and angioedema is not well recognized, partly because the onset of angioedema may be delayed for months or years after commencement of the ACE-I." (See Exhibit 09-83006).

Applicants assert that the inclusion of an ACE inhibitor together as one of many components in a single dosage form would further obscure the recognition of such problems, make them yet more perplexing, and have potential for inadvertent dosing.

The following articles disclose that beta-blockers, a component of the present invention, elevate the risk and severity of anaphylactic and anaphylactoid reactions:

> Lang DM., "Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers." Drug Saf. 1995 May;12(5):299-304. "Studies have demonstrated greater hazards with anaphylaxis in patients receiving beta-blockers." (See Exhibit 10-83006).

> Toogood JH., "Beta-blocker therapy and the risk of anaphylaxis." CMAJ. 1987 May 1;136(9):929-33. "Anaphylaxis ...may be severe, protracted and resistant to conventional treatment because of beta-adrenergic blockade." (See Exhibit 11-83006).

> Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F., "Refractory anaphylactoid shock potentiated by beta-blockers." Cathet Cardiovasc

Diagn. 1996 Dec;39(4):383-4. "We present a case of refractory anaphylactoid shock during coronary angiography in a patient on beta-blockers." (See Exhibit 12-83006)

Because beta-blockers are a component of the present invention, Applicants assert that the addition of an ACE inhibitor, to the present invention, would not only result in a combination that would make the presently overlooked connection between ACE inhibitors and angioedematous reactions yet more puzzling, but would also increase the likelihood of more severe and intractable side-effects.

Applicants have pointed out substantive and material changes that would result from a vasopeptidase inhibitor-containing combination taught by Powell et al. as opposed to the present invention that (by virtue of "consisting essentially of" claim transition) would not contain a vasopeptidase inhibitor. These include increased cardiac morbidity, cardiac mortality, increased restenosis after coronary stenting, and increased potential for severe anaphylactoid side-effects, all due to the interaction of a vasopeptidase inhibitor with a component of the present invention. The combination taught by Powell et al. further substantially differs from the present invention in its potential to cause birth defects if inadvertently dosed during pregnancy. The Applicants also contend that the inclusion of an ACE inhibitor together as one of many components in a single dosage form would, in practice, further obscure the presently overlooked connection between this class of drug and anaphylactoid events.

**Such a combination would be the antithesis of protective.** In view of this contradiction, Powell et al. teach the addition of an ingredient that materially affects the

basic and novel characteristics of Applicants' invention.

Unlike the addition of incipients such as binders and stabilizers that have no effect on the characteristics of Applicants' invention, it is clear from the evidence submitted by Applicants that the increased risks associated with vasopeptidase inhibitors render the addition of vasopeptidase inhibitors in Applicants' invention as materially affecting the basic characteristics of Applicants' claimed invention.

In light of the arguments presented, Applicants respectfully submit that the 35 USC §103(a) rejection of Claims 1-14 has been successfully traversed. Allowance is therefore requested.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 8/30/06

Robert R. Deleault, Reg. No. 39,165
Attorney for Applicants
41 Brook Street
Manchester, NH 03104
Tel. (603) 668-1971
Fax (603) 622-1445

**Certificate of Transmission**

I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office by way of EFS Web on Aug 30, 2006.

Robert R Deleault

# Exhibit 01-83006

Arch Intern Med. 2003 Jul 14;163(13):1574-9.

Aspirin-angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: a dose-related adverse effect of aspirin.

Guazzi M, Brambilla R, Reina G, Tumminello G, Guazzi MD.

Istituto di Cardiologia, Universita degli Studi di Milano, Milan, Italy.
maurizio.guazzi@unimi.it

BACKGROUND: It is debated whether in patients with chronic heart failure (CHF), aspirin may contrast the clinical benefits of angiotensin-converting enzyme inhibitors (ACEIs). Two major unresolved issues in patients with CHF are whether these agents together can affect mortality and whether the interaction is related with the dose of aspirin. We aimed at exploring these possibilities. METHODS: We evaluated more than 4000 hospitalizations with a principal discharge diagnosis of CHF from January 10, 1990, to December 31, 1999. The final analysis was restricted to 344 patients taking ACEIs who satisfied the selection criteria, in whom reliable information was available concerning drug therapy during follow-up. In these patients, treatment included no aspirin in 235 (group 1), a low dose (< or =160 mg) in 45 (group 2), and a high dose (> or = 325 mg) in 64 (group 3). RESULTS: During a mean follow-up of 37.6 months, there were 84 (36%) deaths in group 1, 15 (33%) in group 2, and 35 (55%) in group 3. By the Kaplan-Meier approach, survival was similar in groups 1 and 2, and significantly (P =.009) worse in group 3 compared with groups 1 and 2. After adjusting for potential confounding factors (including treatment, cause of heart disease, age, smoking, and diabetes mellitus), a time-dependent multivariate Cox proportional hazards regression analysis showed that the combination of high-dose aspirin with an ACEI was independently associated with the risk of death (hazard ratio, 1.03; P =.01) and that the combination of low-dose aspirin with an ACEI was not (hazard ratio, 1.02; P =.18). CONCLUSION: These results support the possibility that in some patients with CHF who are taking an ACEI, a dose-related effect of aspirin may adversely affect survival.

# Exhibit 02-83006

Am J Cardiol. 2001 Feb 15;87(4):483-7, A7.

Effect of combined aspirin and angiotensin-converting enzyme inhibitor therapy versus angiotensin-converting enzyme inhibitor therapy alone on readmission rates in heart failure.

Harjai KJ, Nunez E, Turgut T, Newman J.

Department of Cardiology, Ochsner Medical Institutions, New Orleans, Louisiana, USA. kharjai@ochsner.org

An adverse interaction between aspirin and angiotensin-converting enzyme (ACE) inhibitors is suspected in patients with heart failure, but the effect of combined therapy with these agents on hospital readmission rates is unknown. Our study found that combining aspirin with ACE inhibitors is associated with higher early readmission rates than use of ACE inhibitors alone, particularly in patients with depressed ejection fraction and in those without coronary artery disease.

# Exhibit 03-83006

Am J Cardiol. 1997 Jan 15;79(2):115-9.

Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)

Nguyen KN, Aursnes I, Kjekshus J.

Department of Pharmacotherapeutics, University of Oslo, Norway.

The use of angiotensin-converting enzyme (ACE) inhibitors early after an acute myocardial infarction to reduce mortality has been studied in several trials with inconsistent results. Aspirin (ASA) has become a well-documented therapeutic adjunct in patients with coronary heart disease. Attention has recently been focused on a possible interaction between ASA and ACE inhibitors. We therefore reanalyzed data from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) to find any evidence of differential effects of the ACE inhibitor enalapril in subgroups defined by use of ASA at baseline. Logistic regression tested the multiplicative interaction. We used Rothman synergy index S, which would be equal to unity under additivity, and less than unity when suggesting antagonism, to examine the postulated interaction with departure from an additive model. Logistic regression showed that the enalapril-ASA interaction term was a significant predictor of mortality at the end of the study ($p = 0.047$), and was a borderline significant predictor of mortality 30 days after randomization ($p = 0.085$). The Rothman synergy index S was 0.66 (95% confidence interval 0.46 to 0.94) for mortality at the end of the study, and 0.68 ( 0.44 to 1.04) for 30-day mortality, indicating antagonism between enalapril and ASA with departure from an additive model. Thus, we found evidence of enalapril-ASA interaction. The effect of enalapril was less favorable among patients taking ASA than among patients not taking ASA at baseline.

# Exhibit 04-83006

Int Heart J. 2006 Mar;47(2):173-84.

Effects of Angiotensin-Converting Enzyme Inhibitors or an Angiotensin Receptor Blocker in Combination With Aspirin and Cilostazol on In-stent Restenosis.

Ujiie Y, Hirosaka A, Mitsugi M, Ohwada T, et al.

First Department of Internal Medicine, Fukushima Medical University.

It remains to be determined whether adding an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) to antiplatelet therapy has a therapeutic benefit on in-stent restenosis. After successful coronary stenting, 165 patients (167 lesions) were randomly assigned to a basal (aspirin 162 mg + cilostazol 200 mg/day), ACEI (basal treatment + quinapril 10 mg or perindopril 4 mg/day), or ARB (basal treatment + losartan 50 mg/day) treatment group. Quantitative coronary angiography was performed before, immediately following, and 6 months after stenting. Follow-up coronary angiography was completed in 126 patients (128 lesions). Restenosis rates tended to be higher (12, 26, and 12% for the basal, ACEI, and ARB groups, respectively), and target lesion revascularization rates were higher in the ACEI group than in the other groups (9, 23,* and 5%, respectively, *P < 0.05 versus basal group). Moreover, late lumen loss was higher in the ACEI group than in the basal group (0.60 +/- 0.55, 0.98 +/- 0.61* and 0.73 +/- 0.64 mm in the basal, ACEI, and ARB groups, respectively). The combinations of an ACEI or ARB with aspirin and cilostazol are ineffective for the prevention of in-stent restenosis, and an ACEI may even promote intimal proliferation after stent implantation.

# A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*


## ABSTRACT

*Background* Actions of angiotensin II may contribute to the progression of heart failure despite treatment with currently recommended drugs. We therefore evaluated the long-term effects of the addition of the angiotensin-receptor blocker valsartan to standard therapy for heart failure.

*Methods* A total of 5010 patients with heart failure of New York Heart Association (NYHA) class II, III, or IV were randomly assigned to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined end point of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours.

*Results* Overall mortality was similar in the two groups. The incidence of the combined end point, however, was 13.2 percent lower with valsartan than with placebo (relative risk, 0.87; 97.5 percent confidence interval, 0.77 to 0.97; P=0.009), predominantly because of a lower number of patients hospitalized for heart failure: 455 (18.2 percent) in the placebo group and 346 (13.8 percent) in the valsartan group (P<0.001). Treatment with valsartan also resulted in significant improvements in NYHA class, ejection fraction, signs and symptoms of heart failure, and quality of life as compared with placebo (P<0.01). In a post hoc analysis of the combined end point and mortality in subgroups defined according to base-line treatment with angiotensin-converting–enzyme (ACE) inhibitors or beta-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.

*Conclusions* Valsartan significantly reduces the combined end point of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. However, the post hoc observation of an adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE inhibitor, and a beta-blocker raises concern about the potential safety of this specific combination. (N Engl J Med 2001;345:1667-75.)




PHARMACOTHERAPY for heart failure has advanced considerably in recent years as clinical trials have demonstrated favorable long-term effects of angiotensin-converting–enzyme (ACE) inhibitors[1-3] and beta-blockers[4-6] on morbidity and mortality. Despite the use of these potent drugs, heart failure remains the leading reason for hospitalization in the Medicare population,[7] mortality among patients with heart failure is high, and the quality of life is low.

Angiotensin II, a potent vasoconstrictor and growth-stimulating hormone, may contribute to the impairment of left ventricular function and the progression of heart failure through increased impedance of left ventricular emptying,[8] adverse long-term structural effects on the heart and vasculature,[9] and potentially deleterious activation of other neurohormonal agonists, including norepinephrine, aldosterone, and endothelin.[10] Since previous studies have shown that physiologically active levels of angiotensin II persisted despite long-term therapy with an ACE inhibitor,[11,12] we undertook a study to determine whether the angiotensin-receptor blocker valsartan could further reduce morbidity and mortality among patients who were already receiving the pharmacologic therapy that was considered optimal by their physicians. Descriptions of the rationale for and design of this trial have been published elsewhere.[13]

## METHODS

### Study Design

The Valsartan Heart Failure Trial (Val-HeFT) was a randomized, placebo-controlled, double-blind, parallel-group trial. Patients at 302 centers in 16 countries gave written informed consent for participation in the trial, which was approved by the institutional review board at each center. The investigation conformed to the principles of the Declaration of Helsinki. Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals. An independent end-points committee adjudicated all reports of primary end points. An independent data and safety monitoring board reviewed biannual interim analyses. The manuscript was prepared by the authors and reviewed by the steering committee and the sponsor.

### Eligibility

Men and women 18 years old or older with a history and clinical findings of heart failure for at least three months before screening were eligible. Patients had heart failure of New York Heart Association (NYHA) class II, III, or IV and were clinically stable. To be eligible, they had to have been receiving for at least two weeks a fixed-dose drug regimen that could include ACE inhibitors, diuretics, digoxin, and beta-blockers. In addition, they had to have documented left ventricular dysfunction with an ejection fraction of less than 40 percent and left ventricular dilatation with an echocardiographically measured short axis internal dimension at end diastole greater than 2.9 cm per square meter of body surface area.

From the Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis (J.N.C.); and the Mario Negri Institute, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, Milan, Italy (G.T.). Address reprint requests to Dr. Cohn at the Cardiovascular Division, Mayo Mail Code 508, University of Minnesota Medical School, 420 Delaware St., SE, Minneapolis, MN 55455.

*The investigators are listed in the Appendix.

Echocardiograms were analyzed locally after the technical and reader quality at each center had been validated by one of three core laboratories (in Los Angeles; Milan, Italy; or Stockholm, Sweden) that also monitored quality control during the study. Criteria for exclusion have been published previously.[13]

### Placebo Run-in Period

Patients were assessed for two to four weeks to confirm their eligibility, clinical stability, and compliance while taking placebo in a single-blind fashion twice daily. Base-line evaluations included laboratory tests for hematologic variables and blood chemistry; urinalysis; echocardiography; 12-lead electrocardiography; and chest radiography. Quality of life was assessed with the Minnesota Living with Heart Failure questionnaire, which was administered to 60 percent of patients — that is, those in the United States, the United Kingdom, Australia, and Italy.

### Randomization and Dose Adjustment

Eligible patients, stratified according to whether or not they were receiving a beta-blocker as background therapy, were randomly assigned to receive oral valsartan or matching placebo. Stratification was performed to ensure the equal distribution of patients receiving these drugs in the two groups. Randomization occurred after the base-line eligibility data were verified by the coordinating centers in Minneapolis and Milan. Valsartan was initiated at a dose of 40 mg twice daily, and the dose was doubled every two weeks until a target dose of 160 mg twice daily was reached. Placebo doses were similarly adjusted. The criteria for increasing the dose included a systolic blood pressure of 90 mm Hg or higher while the patient was standing, the absence of symptoms of hypotension, and a serum creatinine concentration of less than 2.0 mg per deciliter (177 μmol per liter) or no more than 50 percent higher than the base-line concentration. Patients returned for follow-up visits at two, four, and six months and every three months thereafter.

### Outcome Measures

The study was designed with two primary end points: mortality and the combined end point of mortality and morbidity, which was defined as cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. Secondary cardiovascular outcomes included the changes from base line to the last available observation after treatment had begun in ejection fraction, NYHA functional class, quality-of-life scores, and signs and symptoms of heart failure.

### Statistical Analysis

Statistical analyses were performed at an overall significance level of 0.05, adjusted for the two primary end points. Each primary end point was tested at a two-sided significance level of 0.02532, on the basis of the Dunn–Sidak inequality: $\alpha' = 1-(1-\alpha)^{1/2}$. The significance level for the analysis of the time to death was further adjusted for five biannual interim analyses according to the O'Brien–Fleming alpha-spending function. Therefore, the final analysis for the time to death was performed at a two-sided significance level of 0.02.

The calculation of sample size was based on the time-to-death end point. The number of deaths that would be required to detect, with 90 percent power, a 20 percent difference between the death rate with valsartan and that with placebo (estimated at 12 percent per year) was calculated to be 906. We planned to enroll 2500 patients per treatment group.

Comparisons of the primary end points between treatment groups were performed by means of a log-rank test. To estimate the size of the effect, we used a Cox regression model with prespecified base line covariates, including NYHA class, ejection fraction (above or below the median), cause of heart failure (ischemic or nonischemic), age (younger than 65 years or 65 years old or older), ACE inhibitor use or nonuse, and beta-blocker use or nonuse. Confidence intervals of 98 percent and 97.5 percent were calculated for mortality and the combined end point of mortality and morbidity, respectively. To estimate the size of the effect on the secondary end points and in subgroups, relative risks with 95 percent confidence intervals were calculated with the use of the Cox regression model.

## RESULTS

Of the 5010 patients who underwent randomization, 2511 were assigned to receive valsartan and 2499 to receive placebo, all with background therapy for heart failure. There were no clinically relevant differences in the base-line characteristics of the two groups (Table 1). A description of the base-line demographic characteristics of this diverse population has been published previously.[14] At the time of randomization, 93 percent of the patients were being treated with ACE inhibitors. The average daily doses were 17 mg of enalapril, 19 mg of lisinopril, 80 mg of captopril, 6 mg of ramipril, and 23 mg of quinapril. Thirty-five percent of the patients were receiving beta-blockers (15 percent were receiving carvedilol, 12 percent metoprolol, and 3 percent atenolol), and randomization was stratified according to their use or nonuse; this percentage remained stable throughout the study. Only 5 percent of the patients were treated with spironolactone. The overall mean duration of follow-up was 23 months (range, 0 to 38).

The target dose was achieved in 84 percent of the patients receiving valsartan (mean dose, 254 mg) and 93 percent of those receiving placebo (mean equivalent dose, 283 mg). Systolic blood pressure was reduced to a greater extent with valsartan than placebo: at four months, it was reduced by a mean (±SD) of 5.2±15.8 mm Hg in the valsartan group, as compared with 1.2±14.8 mm Hg in the placebo group, and at one year the reductions were 5.2±16.0 mm Hg and 1.3±15.9 mm Hg, respectively. The mean heart rate was unchanged.

### Primary End Points

Mortality was similar in the two treatment groups (Fig. 1 and Table 2). The adjudicated causes of death were also similar in the two treatment groups (there were 262 sudden deaths from cardiac causes in the valsartan group and 258 in the placebo group, and there were 118 deaths due to heart failure in the valsartan group and 125 in the placebo group).

The combined end point of mortality and morbidity was significantly reduced among patients receiving valsartan as compared with those receiving placebo ($P=0.009$) (Fig. 2). The benefit appeared early after randomization and increased throughout the trial. Among the patients in the valsartan group, 723 (28.8 percent) reached the combined end point, as compared with 801 patients (32.1 percent) in the placebo group — a 13.2 percent reduction in risk with valsartan (relative risk, 0.87; 97.5 percent confidence interval, 0.77 to 0.97) (Table 2). The pre-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT GROUP.*

| CHARACTERISTIC | VALSARTAN GROUP (N=2511) | PLACEBO GROUP (N=2499) |
|---|---|---|
| Age (yr) | 62.4±11.1 | 63.0±11.0 |
| Male sex (% of patients) | 79.9 | 80.0 |
| Race (% of patients) | | |
| White | 89.8 | 90.9 |
| Black | 7.2 | 6.5 |
| Other | 2.9 | 2.6 |
| Primary cause of heart failure (% of patients) | | |
| Coronary heart disease | 57.6 | 56.8 |
| Idiopathic | 31.1 | 31.2 |
| Hypertension | 6.1 | 7.3 |
| Other | 5.2 | 4.7 |
| NYHA class (% of patients)† | | |
| II | 62.1 | 61.4 |
| III | 36.1 | 36.3 |
| IV | 1.7 | 2.2 |
| Diabetes (% of patients) | 25.9 | 25.1 |
| Atrial fibrillation (% of patients) | 12.0 | 12.2 |
| Ejection fraction (%) | 26.6±7.3 | 26.9±7.0 |
| Left ventricular internal diastolic diameter (cm/m²) | 3.7±0.5 | 3.7±0.5 |
| Blood pressure (mm Hg) | | |
| Systolic | 123.0±18.4 | 124.0±18.6 |
| Diastolic | 76.0±10.5 | 76.0±10.7 |
| Background therapy (% of patients) | | |
| Diuretic | 85.8 | 85.2 |
| Digoxin | 67.1 | 67.6 |
| Beta-blocker | 34.5 | 35.3 |
| ACE inhibitor | 92.6 | 92.8 |

*Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

†Five patients who were found to be in New York Heart Association (NYHA) class I are not shown.

dominant benefit in terms of the combined end point was a 24 percent reduction in the rate of adjudicated hospitalizations for worsening heart failure as a first event in those receiving valsartan (13.8 percent) as compared with those receiving placebo (18.2 percent) ($P<0.001$) (Table 2).

### Secondary End Points

The risk of a hospitalization for heart failure (with censoring of the data for patients who died) was reduced by 27.5 percent with valsartan ($P<0.001$). There were 1189 nonadjudicated hospitalizations for heart failure in the placebo group and 923 in the valsartan group ($P=0.002$). Since hospitalizations for problems other than heart failure were unaffected, the rate of hospitalizations for any cause was reduced similarly — by 250 events, from 3106 in the placebo group to 2856 in the valsartan group ($P=0.14$). The mean change in ejection fraction from base line to the last observation was 4.0 percent in the valsartan group and 3.2 percent in the placebo group ($P=0.001$). More patients in the valsartan group than in the placebo group had improvements in NYHA classification (23.1 percent vs. 20.7 percent) and fewer had worsening (10.1 percent vs. 12.8 percent) ($P<0.001$). Similarly, dyspnea, fatigue, edema, and rales were more favorably affected by valsartan than by placebo ($P<0.01$). Among the 1504 patients in the valsartan group to whom the Minnesota Living with Heart Failure questionnaire was administered, there was little change in scores from base line to the end point, but among the 1506 such patients in the placebo group, the mean score worsened by an average of 1.9 ($P=0.005$ for the comparison between the treatment groups).

### Subgroup Analyses

The beneficial effect of valsartan on the combined mortality–morbidity end point was generally consistent among the predefined subgroups of patients. Valsartan improved the outcome in young and old patients, men and women, those with and without diabetes or coronary artery disease, those with ejection fractions or left ventricular dimensions above and below the median, and those with NYHA class II and class III or IV symptoms (Fig. 3). In the small, heterogeneous black population (which included 344 African-American and South African patients), there was a wide confidence interval for relative risk of the combined end point with valsartan that included 1.0 (relative risk, 1.11; 95 percent confidence interval, 0.77 to 1.61).

Background therapy with neurohormonal inhibitors appeared to influence the response to valsartan (Fig. 4). The patients were divided into four subgroups on the basis of the use or nonuse of ACE-inhibitor and beta-blocker therapy at base line. The global test for the interaction between treatment and subgroup among the four subgroups was statistically significant for mortality ($P=0.009$) and the combined end point of mortality and morbidity ($P=0.001$). In the three groups receiving neither drug or either ACE inhibitors or beta-blockers alone, there was a significantly favorable effect of valsartan on the rate of the combined end point ($P=0.003$, $P=0.002$, and $P=0.037$, respectively) and a favorable point estimate of the odds ratio for death. Mortality was significantly reduced in the 226 patients who were treated with neither an ACE inhibitor nor a beta-blocker ($P=0.012$). Among those who were receiving both drugs at base line, valsartan had an adverse effect on mortality ($P=0.009$) and was associated with a trend toward an increase in the combined end point of mortality and morbidity ($P=0.10$). Among all 366 patients who were not receiving an ACE inhibitor, whether or not a beta-blocker had been prescribed, there was a significantly lower risk of the combined end point in the valsartan group than in the placebo group (rel-

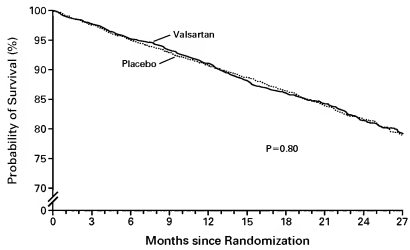


**Figure 1.** Kaplan–Meier Analysis of the Probability of Survival.

**TABLE 2.** INCIDENCE AND RELATIVE RISK OF THE PRIMARY END POINTS.

| EVENT | VALSARTAN GROUP (N=2511) | PLACEBO GROUP (N=2499) | RELATIVE RISK (CI)* | P VALUE† |
|---|---|---|---|---|
| | no. with event (%) | | | |
| Death from any cause (during entire trial) | 495 (19.7) | 484 (19.4) | 1.02 (0.88–1.18) | 0.80 |
| Combined end point | 723 (28.8) | 801 (32.1) | 0.87 (0.77–0.97) | 0.009 |
| Death from any cause (as first event) | 356 (14.2) | 315 (12.6) | | |
| Hospitalization for heart failure | 346 (13.8) | 455 (18.2) | | |
| Cardiac arrest with resuscitation | 16 (0.6) | 26 (1.0) | | |
| Intravenous therapy | 5 (0.2) | 5 (0.2) | | |

*The 98 percent confidence interval (CI) was calculated for the mortality end point (death from any cause), and the 97.5 percent confidence interval was calculated for the combined mortality–morbidity end point.

†P values were calculated by the log-rank test from time to first event.

ative risk, 0.56; 95 percent confidence interval, 0.39 to 0.81), as well as a lower risk of death (relative risk, 0.67; 95 percent confidence interval, 0.42 to 1.06).

### Safety

Valsartan therapy was generally well tolerated. Adverse events leading to the discontinuation of the drug occurred in 249 of the patients receiving valsartan (9.9 percent) and 181 patients receiving placebo (7.2 percent) ($P<0.001$). The adverse events leading to discontinuation and occurring in more than 1 percent of the patients in the valsartan group included dizziness (in 1.6 percent of the patients and 0.4 percent of those in the placebo group; $P<0.001$), hypotension (1.3 percent and 0.8 percent, respectively; $P=0.124$), and renal impairment (1.1 percent and 0.2 percent, $P<0.001$). Overall, the mean change from base line in the blood urea nitrogen concentration was an increase of 5.9 mg per deciliter (2.1 mmol per liter) with valsartan and an increase of 3.3 mg per deciliter (9.2 mmol per liter) with placebo ($P<0.001$). The mean change in the serum creatinine concentration was an increase of 0.18 mg per deciliter (15.9 $\mu$mol per liter) with valsartan and an increase of 0.10 mg per deciliter (8.8 $\mu$mol per liter) with placebo ($P<0.001$). The mean change in the serum potassium concentration was an increase of 0.12 mmol per liter with valsartan and a decrease of 0.07 mmol per liter with placebo ($P<0.001$).

## DISCUSSION

Our study was designed to assess the efficacy of the angiotensin-receptor blocker valsartan when add-

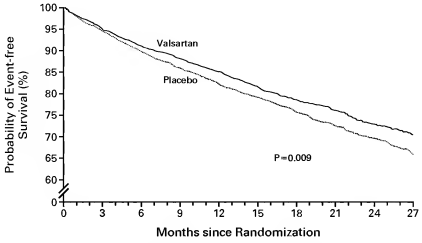


**Figure 2.** Kaplan–Meier Analysis of the Probability of Freedom from the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators).

ed to prescribed therapy for heart failure. The benefit in terms of morbidity and mortality was achieved in a population in which 93 percent of patients were treated with an ACE inhibitor and 35 percent were treated with a beta-blocker. The outcomes suggest that even with the use of currently prescribed therapy, angiotensin contributes to morbidity but not mortality in patients with heart failure. An unexpected finding emerged, however, from a post hoc analysis of the data on concomitant therapy. Within the 30 percent of the population that was being treated with both an ACE inhibitor and a beta-blocker at base line, there was a significant adverse effect of valsartan on mortality and a nearly significant adverse effect on morbidity. Clarification of whether this finding represents a true interaction or is attributable to chance must await the outcome of ongoing trials evaluating the combination of an angiotensin-receptor blocker with an ACE inhibitor and a beta-blocker. Since only 5 percent of the patients in the trial were receiving spironolactone, an aldosterone-receptor blocker,[15] we cannot assess the efficacy or safety of valsartan when given in combination with spironolactone.

The protocol was designed with two primary end points and appropriate statistical adjustment. Although mortality was similar in the two treatment groups, a significant favorable effect of valsartan on cardiovascular morbidity was evident, primarily as a result of a 24 percent reduction in adjudicated (first) hospitalizations for heart failure and a similar reduction in all nonadjudicated (subsequent) hospitalizations for heart failure. The favorable effect was achieved with a target dose of 160 mg twice daily; this dose was chosen because of its hemodynamic and hormonal effects, which were documented in a pilot study involving patients who were receiving ACE-inhibitor therapy.[16] The dose was well tolerated; most patients achieved the target dose, and side effects were only slightly more prevalent than in the placebo group.

This study differed from previous trials of angiotensin-receptor blockers in heart failure, such as the Losartan Heart Failure Survival Study[17] and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction,[18] in terms of the high dose we used, our large sample size, and the use of valsartan as a balanced, placebo-controlled add-on to background therapy.

The reduction in cardiovascular morbidity has relevance for the economic burden of heart failure on the health care system. In addition, the moderate but statistically significant benefit in terms of the secondary end points — NYHA class, quality of life, signs and symptoms of heart failure, and left ventricular ejection fraction — is consistent with an overall incremental benefit of valsartan for patients with heart failure who are receiving medical therapy.

The negative effect of angiotensin II on heart failure could be mediated through a vasoconstrictor-induced increase in blood pressure or a direct effect on cardiac and vascular tissues. Since systolic blood pressure was an average of 5 mm Hg lower in patients who were randomly assigned to receive valsartan than in those assigned to receive placebo, a hemodynamic mechanism may account, at least in part, for the observed benefit. Nonetheless, the growth-promoting and apoptotic effects of angiotensin II have been well demonstrated[9,19] and may contribute to the structural remodeling that promotes the progression of heart

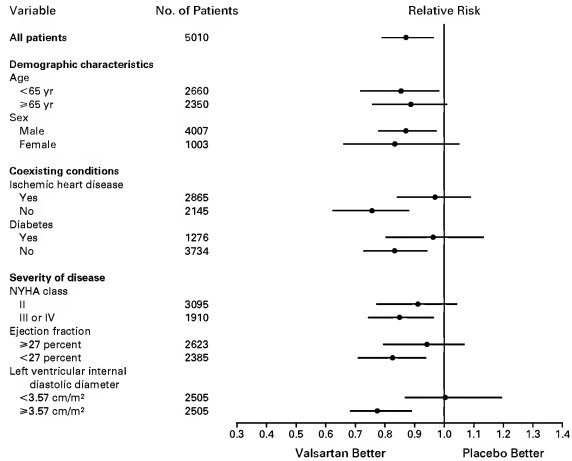


**Figure 3.** Relative Risks and 95 Percent Confidence Intervals for the Combined End Point, According to Demographic and Clinical Characteristics.

Patients found to be in New York Heart Association (NYHA) class I were not included in the analysis of severity of disease. Two patients did not have an ejection-fraction measurement at base line.

failure.[20-24] A long-term increase in the ejection fraction has been identified as a marker of regression of left ventricular remodeling that is manifested as reduced chamber volume.[25,26] This structural effect has been associated with an improvement in survival.[27,28] In our study, the increase in the ejection fraction was more moderate than in previous trials of ACE inhibitors and beta-blockers and was not associated with reduced mortality. The absence of a more robust effect may be related to the effectiveness of the other therapy received by the patients (annual mortality in the placebo group was 9 percent, rather than the predicted 12 percent).

Subgroup analysis is used in large-scale trials to confirm the generalizability of the findings or, if inconsistencies are observed, to generate hypotheses about subgroup responses to be tested in subsequent studies. In our study, subgroups defined on the basis of demographic characteristics or base-line clinical characteristics generally had responses that were similar to those in the study population as a whole. Background neurohormonal-inhibitor therapy, however, appeared to influence the outcome. Since this background therapy was not controlled and patients were only partially stratified according to its presence or absence at randomization (according to the use of beta-blockers but not ACE inhibitors), the data generated by this analysis must be interpreted with caution. Nonetheless, in the small subgroup of patients (7 percent) who were not being treated with an ACE inhibitor, there was a 44.0 percent reduction in the combined end point of mortality and morbidity and a 33.1 percent reduction in mortality.

The point estimate of the odds ratio favored valsartan in all subgroups except the subgroup of patients who were being treated with both an ACE in-

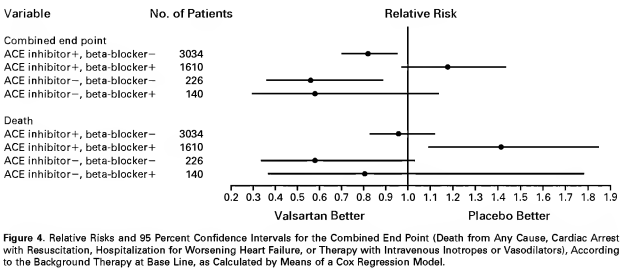


**Figure 4.** Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, as Calculated by Means of a Cox Regression Model.

ACE denotes angiotensin-converting enzyme, + the use of the drug, and − nonuse.

hibitor and a beta-blocker at base line. As previously noted, the apparent adverse effect of valsartan in this subgroup leads to the hypothesis that the extensive blockade of multiple neurohormonal systems in patients with heart failure could be deleterious. Recent clinical-trial experience with moxonidine,[29] endothelin-receptor antagonists, and cytokine inhibitors[30] is consistent with this hypothesis. Several trials involving substantial numbers of patients who are receiving these three classes of neurohormonal inhibitors are ongoing and can be expected to provide additional data relevant to this safety concern.

Although current guidelines recommend ACE inhibitors and beta-blockers as standard therapy for heart failure because of their demonstrated benefit in terms of mortality, only one third of the patients enrolled in our study were receiving both classes of drugs. Furthermore, patients who were already being treated with angiotensin-receptor blockers, which are widely prescribed for patients who are intolerant of ACE inhibitors, were excluded from the study. Improved compliance with the guidelines may reduce the number of inadequately treated patients. Nonetheless, the benefit of valsartan in terms of the combined end point of mortality and morbidity that was found in all subgroups except that receiving both ACE inhibitors and beta-blockers suggests that the drug could have a role in the management of the syndrome.

Supported by a grant from Novartis Pharma, Basel, Switzerland. Drs. Cohn and Tognoni have had research support and consultation arrangements with Novartis Pharmaceuticals, the sponsor of this study.

Presented in part at the American Heart Association meeting, New Orleans, November 12–15, 2000.

## APPENDIX

The Valsartan Heart Failure Trial Investigators included the following: in the United States: Alabama — R. Bourge, D. Calhoun, B. Foley, L. Lowe, S. Oparil, G. Perry, B. Rayburn, B. Sanders; Arizona — J.E. Boulet, J. Christensen, P. Fenster, S. Heumiller, R. Lee, P. McGowan, J. Ohm, R. Siegel, T. Struikmans; California — J.W. Allen, J. Backman, P. Coleman, D. Costello, T.A. Cox, P. Deedwania, L. Defensor, G. Dennish, W.A. Edmiston, D. Everitt, S. Fabbri, C. Faulkner, T. Gilbert, J.I. Gorwitz, S. Harte, L.A. Hawkins, J. Hemphill, J.T. Heywood, B. Jackson, B. Jaski, S. Khan, D. McAdams, P. Pak, N. Parker, R. Shabetai, H. Shively, J. Sklar, L. Sprinkle, R. Stein, P. Waack, R. Wadlington, R. Wright, L.G. Yellen; Connecticut — S. Carolan, I.S. Cohen, M.B. Fowler, M. Martin-O'Brien, A. Mullin, T. Ramahi, R. Rholl; District of Columbia — D.J. Diver, N. Douglas-Kersellious, D. Lee, S. Singh; Florida — J. Anderson, J. Bauerlein, M. Bayer, G. Cintron, S. Brenner, C. Davenport, S.L. Duncan, P. Green, T.C. Hilton, H. Karunaratne, A. Kinsella, G. Lamas, M. Mayor, M. McIvor, M.R. Mihuski, M.A. Nocero, J. O'Bryan, J. Reddinger, D. Samada, C.R. Stastny, M. Taylor, H. Tee, J.L. Walker, V. Wilson; Georgia — S. Beer, A. Carr, J. Grace, J. Guidot, S. Holt, K. Taylor, W.R. Taylor, P. Yaun; Illinois — K. Furlong, M. Johnson, R. Lang, H. Loeb; Indiana — J. Becker, J. Birt, L. Ford; Iowa — R. Oren, P. Scovall, W. Wickemeyer, N. Young; Kansas — M. Bowles; Kentucky — K. Doerschuk, S. Wagner; Louisiana — B. Ineld; Maryland — L. Black, S. Gottlieb, S.O. Gottlieb, N. Greenberg, D. Lowry; Massachusetts — A. Burger, M. Burger, K. Coleman, M. Grisaia, W. Dec, C. Haggan, T. Meyer, M. Morra, P. Shrewe, J. Smith; Michigan — P.A. Kaminski, D. Langholz, A.B. Levine, T.B. Levine, J. Nicklas, R. Rose; Minnesota — I. Anand, S. Berg, A. Holmstrom, B. Merkle, L. Miller; Missouri — K. Aggarwal, E. Geltman, M. Gilbert, B. Lee, C. Hinden, D. Yip; Nevada — A. Cason-Fitcher, R. Croke, A. Stelljes; New Jersey — R. Berkowitz, H.S. Ribner, J. Strobeck, P. Tabachnik, M.J. Zucker; New Mexico — M. Conway, P. Doherty, R. Dubroff, S. Justice; New York — M. Applegate, L. Baruch, C. Buchholz-Varley, J. Cappelli, M.E. Coglianese, J. Corbelli, T. Costantino, M.A. Goodman, S. Graham, V. Hart, M. Kukin, O. Ocampo, W. Orlowski, P. Paracsli, N. Schulhoff, P. Stein, R.M. Steingart, B.H. Sung, M.F. Wilson; North Carolina — R. Bilbro, F. Cobb, G. Dodson, D. Framm, K. Harshaw Ellis, M. Higginbotham, B. Kuzil, G. Weidner; Ohio — D.J. Kerciakes, R. Lengerich, L.L. Wohlford; Oklahoma — J. Anderson, J. Cook, M. Dickson, R.D. Easley, S. Jamieson, J. Kallbfleisch, C. Melson-Alsip, D. Simmons; Oregon — R. Hershberger, L. Kelson; Pennsylvania — M. Amidi, M. Bell, J. Boehmer, E. Loh, P.J. Mather, S. Rubin, R. Shannon, I. Smith, R. Weller Moore, S. Worley; Rhode Island — A. Sadani-antz, South Carolina — J. Evans, G. Hendrix; Tennessee — L. Chitmark, W.G. Friesen, S. Gubin, L. Howerton, J. Jeanes, F. McGrew, J. Osborn, K.B. Ramanathan, R. Smith; Texas — N. Baradhi, L.A. Campos, R. Carney, S.B. El Hafi, R. Gammon, J.D. Jackman, C. Janes, D. McCarroll, F.

Navetta, M. Rottman, A. Smith; Utah — J.J. Perry; Virginia — J. Bergin, J. Herre, J. O'Brien; Washington — B. Crane, D. Fishbein, J. Forster, M. Hall; Wisconsin — C.V. Hughes, J. Hoseinpud, R. Siegel, C.R. Vander Ark, P.A. Wiederholt; outside the United States: Australia — J. Amerena, I. Button, R. Calvert, M. Croot, P. Garraby, C. Hall, H. Hankey, D. Hogan, D. Hollens-Riley, J. Horowitz, L. Howes, B. Jackson, I. Jeffrey, J. Karrasch, S. Leslie, H. Krum, L. Martin, B. Singh, P. Taverner, A. Thomson, P. Thompson; Belgium — S. Degré, P. De Vusser, W. Droogné, P. Noyens, A.Z.J. Paltijn, A. Strijckmans, J. Vanhaecke, W. Van Mieghem, J. Vanveldeen; Czech Republic — R. Cífková, J. Gregor, J. Simon, J. Toman, J. Vojacek, J. Widimsky; Denmark — O. Gotzsche, L. Hagdrup, P. Hildebrandt, E. Kassis, T. Tofteguard Nielsen; Finland — E. Engblom, J. Hartikainen, S. Majahalme, M. Niemelä, K. Peuhkurinen, M. Pietilä, J. Taurio, L.-M. Voipio-Pulkki; France — P. Lechat, M. Baudet, M. Bory, A. Cohen, P. Courcel, M. Dahan, J.M. Davy, Y.M. Frances, M. Galinier, M. Guechiche, G. Jarry, J.P. Ollivier, L. Slimane, M. Zaouali; Germany — C. Bergmeier, K.O. Bischoff, C.G. Brilla, J. Cyran, W.G. Daniel, M. Dürsch, E. Fleck, L. Goedel-Meinen, R. Griebenow, R. Hambrecht, M. Hamel, K.H. Hauff, G. Haustein, C. Helzer-Arbeiter, D. Hey, T. Ineefs, M. Hofmann, T. Kleemann, D. Koch, N. Kokott, T. Langenickel, E. Lopez, T. Matthes, V. Mitrovic, E. Mueser, K.H. Munderloh, S. Philipp, V. Regitz-Zagrosek, A. Rouwen, R. Rummel, A. Schmidt, J. Senges, K. Stumpe, H. Topp, C. Weiler, R. Willenbrock, S. Winkler; Hungary — M. Csanady, I. Edes, K. Farkas, C. Farsang, T. Forster, T. Fulop, A. Ianosi, L. Mezei, A. Nemeth, E. Palkovi, E. Seigeti; Italy — M.C. Albanese, G. Alunni, G. Ansalone, B. Aloisi, L. Belloni, R. Belluschi, D. Bertoli, I. Bisceglia, G.M. Boffa, E. Bosi, A. Branzi, E. Butti, L. Cacciavillani, C. Campana, S. Capomolla, G. Castiglioni, A. Cavalli, V. Ceci, F. Cerè, V. Cernicione, F. Cobelli, G. Corsini, A. L. Cazzato, F. De Santis, G. Di Pasquale, M. Farruggio, C. Fresco, G. Ferrari, G. Fiorizzo, G. Foti, A. Fraticelli, P.A. Galati, K. Ghebremariam-Tesfau, F. Giancotti, P. Giannuzzi, G. Gibelli, A. Giordano, E. Giovannini, S. Graziani, F. Ingrilli, S. Lombroso, P. Longaro, L. Magliani, C. Manes, R. Mangia, G. Misuraca, R. Mocchegiani, A.P. Morciano, G. Occhi, M. Oliverì, M. Palvarini, R. Pancarola, L. Pasetti, S. Pede, R. Pedretti, G.P. Perini, F. Pertticone, G. Pertinati, F. Plastina, M. Porcu, C. Porcellati, F. Pozzar, C. Pulignano, C. Rapezzi, F. Rasconi, A. Sanna, M. Santini, V. Santoro, S. Scalvini, F. Scapellato, A.M. Schillaci, C. Schweiger, G. Sinagra, D. Staniscia, P. Tanzi, L. Tavazzi, E. Uslenghi, G. Ventura, A. Vetrano, E. Zanelli; the Netherlands — M. Baseler, P. Bruels, P.W.F. Bruggink, P. Den Hartog, P. Dunselman, P. Pels, G. Geens, H. Greeneveld, B. Hamer, N. Helwerda, J. Kragten, G. Laarman, J. Levert, A. Liem, P. Lindner, H.R. Michels, G. Paulussen, J.L. Posma, H.J. Schaafsma, W.M. Siesverda, L.C. Slegers, P. van der Burgh, E.C.M. van der Velden, A.J.J. van Es, L. van Kempen, H. van Kesteren, R. van Lijswijk, P. van Rossum, D.J. Heijden, J.C.L. Westdorp, A. Willems, A. Withagen; Norway — M. Bjurstroem, A. Herwald, T.O. Klemsdal, K. Knutsen, T. Lappegaard, S. Solheim, S. Toft, K.V. Taseth, A. Westheim, T. Wessel-Aas; South Africa — L.J. Burgess, P.J. Commerford, Y. Govender, E. Klug, P. Manga, F. Muritz, D.P. Naidoo, L. Opie, H.W. Prozesky, D. Smith; Spain — A. Agustí Llopis, E. Asín Cardiel, V. Barrios Alonso, A. Bayes De Luna, J. Bayon Fernandez, J.L. Diago Torrent, E. Galve Basilio, M. Gil De La Peña, M. Gómez Gerboles, E. Homs Espinach, I. Iglesias Garriz, J. Julio Cibergans, A. López Granados, A. Mallol Kirchner, N. Manito Lorite, R. Masa Martorell, J. Orna, J. Pedro Balmaña, F. Pérez Villa, J. Roca Elias, E. Roig Minguell, J. Soler Soler, F. Valles Beluse; Sweden — A. Andersson, H. Broderson, S. Ekdahl, J. Ellström, S. Hansen, J. Herlitz, L. Hjelmaeus, C. Höglund, B. Karlsson, P. Karzman, L. Ljungdahl, M. Lundblad, H. Tygesen, C. Wettervik, L. Winberg; United Kingdom — A. Balsi, A. Blackwell, C. Cope, D. Connelly, T.R. Cripps, G. Dadahl, M.K. Ghosh, S. Gibbs, S. Gupta, M.E. Heber, P.J.B. Hubner, G.D. Johnston, N. Jones, J. Kooner, R. Levy, D. Lubel, P. Nicholls, A. Rodriguez, P. Schofield, E. Smith, J.B. Squire, L.B. Tan, C. Welsh, S. Williams; Executive Committee — J.N. Cohn (chair), G. Tognoni (co-chair), R.D. Glazer, D. Spormann; Steering Committee — J.N. Cohn (chair), G. Tognoni (co-chair), H. Krum, J. Vanhaecke, J. Widimsky, T. Haghfelt, S. Majahalme, P. Lechat, K. Stumpe, L. Tan, C. Farsang, L. Tavazzi, N.J. Helwerda, A. Westheim, L. Opie, A. Bayes de Luna, C. Höglund, I. Anand; Study Coordination Centers — S. Ziesche, R. Latini, A.P. Maggioni; End-Point Committee — P. Carson (chair), C. Opasich, M. Scherillo, G. Sinagra, A. Volpe, C. O'Connor, I. Piña, F. Tristani, L.W. Stevenson; Data Safety Monitoring Board — W. Parmley (chair), M. Bobbio, D.J. van Veldhuisen, J. Abrams, D. DeMets; Echo Core Laboratory — M. Wong, C. Höglund, L. Staszewsky, A. Volpi; Neurohormone Laboratory — D. Judd, R. Latini, S. Masson.

## REFERENCES

**1.** The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

**2.** The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

**3.** Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

**4.** CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet 1999;353:9-13.

**5.** MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.

**6.** Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.

**7.** Popovic JR, Kozak LJ. National Hospital Discharge Survey: annual summary, 1998. Vital and health statistics. Series 13. No. 148. Washington, D.C.: Government Printing Office, September 2000. (DHHS publication no. (PHS) 2000-1719.)

**8.** Cohn JN. Vasodilator therapy for heart failure: the influence of impedance on left ventricular performance. Circulation 1973;48:5-8.

**9.** Dzau VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. Arch Intern Med 1993;153:937-42.

**10.** Jilma B, Krejcy K, Dirnberger E, et al. Effects of angiotensin-II infusion at pressor and subpressor doses on endothelin-1 plasma levels in healthy men. Life Sci 1997;60:1859-66.

**11.** Kawamura M, Imanashi M, Matsushima Y, Ito K, Hiramori K. Circulating angiotensin-II levels under repeated administration of lisinopril in normal subjects. Clin Exp Pharmacol Physiol 1992;19:247-50.

**12.** Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. Circulation 2000;101:844-6.

**13.** Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A. Rationale and design of the Valsartan Heart Failure trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. J Card Fail 1999;5:155-60.

**14.** Cohn JN, Tognoni G, Glazer R, Spormann D. Baseline demographics of the Valsartan Heart Failure Trial. Eur J Heart Fail 2000;2:439-46.

**15.** Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.

**16.** Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin-converting enzyme inhibitor therapy in patients with heart failure. Circulation 1999;99:2658-64.

**17.** Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial — the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582-7.

**18.** McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. Circulation 1999;100:1056-64.

**19.** Leri A, Liu Y, Li B, et al. Up-regulation of $AT_1$ and $AT_2$ receptors in postinfarcted hypertrophied myocytes and stretch-mediated apoptotic cell death. Am J Pathol 2000;156:1663-72.

**20.** Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling — concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35:569-82.

**21.** Dostal DE, Baker KM. Angiotensin II stimulation of left ventricular hypertrophy in adult rat heart: mediation by the $AT_1$ receptor. Am J Hypertens 1992;5:276-80.

**22.** Harrap SB, Dominiczak AF, Fraser R, et al. Plasma angiotensin II, predisposition to hypertension, and left ventricular size in healthy young adults. Circulation 1996;93:1148-54.

**23.** Jacobi J, Schlaich MP, Delles C, Schobel HP, Schmieder RE. Angiotensin II stimulates left ventricular hypertrophy in hypertensive patients independently of blood pressure. Am J Hypertens 1999;12:418-22.

**24.** Crabos M, Roth M, Hahn AWA, Erne P. Characterization of angiotensin II receptors in cultured adult rat cardiac fibroblasts: coupling to signaling systems and gene expression. J Clin Invest 1994;93:2372-8.

**25.** Wong M, Johnson G, Shabetai R, et al. Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure: Veterans Affairs cooperative studies V HeFT I and II. Circulation 1993;87:Suppl VI:VI-65–VI-70.

**26.** Francis GS, Cohn JN. Heart failure: mechanisms of cardiac and vascular dysfunction and the rationale for pharmacologic intervention. FASEB J 1990;4:3068-75.

**27.** Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic sig-

nificance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. Circulation 1993;87:Suppl VIA/I 17–VI 23.
28. Patten RD, Uretsky BF, Konstam MA. Ventricular remodeling and its prevention in the treatment of heart failure. Curr Opin Cardiol 1998;13:162-7.
29. Jones CG, Cleland JGF. Meeting report — the LIDO, HOPE, MOXCON, and WASH studies. Eur J Heart Fail 1999;1:425-31.
30. Louis A, Cleland JGF, Crabbe F, et al. Clinical trials update: CAPRICORN, COPERNICUS, MIRACLE, STAR, RITZ-2, RECOVER, and RENAISSANCE and cachexia and cholesterol in heart failure: high lights of the scientific sessions of the American College of Cardiology, 2001. Eur J Heart Fail 2001;3:381-7.

# Exhibit 06-83006

N Engl J Med. 2006 Jun 8;354(23):2443-51.

Major congenital malformations after first-trimester exposure to ACE inhibitors.

Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, et al.

Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN 37232, USA. william.cooper@vanderbilt.edu

BACKGROUND: Use of angiotensin-converting-enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. We conducted a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations. METHODS: We studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and born between 1985 and 2000 for whom there was no evidence of maternal diabetes. We identified 209 infants with exposure to ACE inhibitors in the first trimester alone, 202 infants with exposure to other antihypertensive medications in the first trimester alone, and 29,096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records. RESULTS: Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02). CONCLUSIONS: Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.

# Exhibit 07-83006

N Z Med J. 2006 Apr 21;119(1232):U1930.

Oral angioedema secondary to ACE inhibitors, a frequently overlooked association: case report and review.

Hurst M. Empson M.

Clinical Immunology Department, Liverpool Hospital, Sydney, NSW, Australia.

---

Ann Ital Med Int. 1997 Jan-Mar;12(1):8-10.

Angioedema due to angiotensin-converting enzyme inhibition: an association frequently unrecognized.

Cicardi M, Conciato L, Agostoni A.

Istituto di Medicina Interna, IRCCS Ospedale Maggiore di Milano.

---

Am J Emerg Med. 1992 Nov;10(6):550-2.

Angiotensin-converting enzyme inhibitor-induced angioedema: still unrecognized.

Finley CJ, Silverman MA, Nunez AE.

Department of Emergency Medicine, Eastern Virginia Graduate School of Medicine, Norfolk 23507.

Angiotensin-converting enzyme inhibitors are a widely used antihypertensive modality. While they have a favorable side effect profile, there is a .1% to .2% incidence of potentially life threatening angioedema. The edema usually presents in the head and neck, especially the face, lips, tongue, and glottis. Patients may initially be treated with standard anti-allergic therapy; however, the situation may dictate a more aggressive therapeutic approach. The authors present the case of a patient who presented with angioedema 18 times over a 3-year period to qualified emergency physicians before the correct diagnosis of angiotensin-converting enzyme inhibitor-induced angioedema was made. Despite recent literature on the subject, there appears to be a lack of familiarization among emergency department physicians regarding this relatively common adverse effect.

---

# Exhibit 08-83006

American Family Physician
A peer-reviewed journal of the American Academy of Family Physicians
September 15, 2002

Late Angioedema Caused by ACE Inhibitors Underestimated

TO THE EDITOR: Angioedema is an uncommon side effect of using angiotensin-converting enzyme (ACE) inhibitors, with an incidence of 0.1 to 0.2 percent.1 It was believed that most cases of angioedema occur within the first week of treatment with ACE inhibitors; however, recent reports1-3 indicate that late-onset angioedema may be more prevalent than initially thought. While early-onset angioedema should not be a diagnostic problem, late-onset angioedema often goes undiagnosed because many physicians are unfamiliar with it.1,4 This oversight may occur because of the lack of a temporal relationship between the use of ACE inhibitors and the onset of angioedema, because this side effect can occur after many years of uneventful use.1,4 Consequently, many patients experience recurrent episodes before the correct diagnosis is made.4 Blacks are at increased risk.3,4

Angioedema associated with the use of ACE inhibitors is not an allergic reaction.2 The pathogenesis is probably related to the increased levels of bradykinins; however, an exclusive role of bradykinins is unlikely.1 Less frequently, angioedema has been reported with angiotensin-receptor antagonists which lack the bradykinin-potentiating activity.2

The clinical presentation is highly variable and unpredictable. In most cases, the symptoms are mild and regress spontaneously while the patient continues the medication, thus erroneously prompting an alternative diagnosis.4 If the diagnosis is missed, recurrent and more severe episodes may occur with potentially serious consequences.4 Fatal cases have also been described.5

Angioedema associated with the use of ACE inhibitors usually presents as episodic attacks of swelling of the face, tongue, and airways, but it may also involve visceral tissues. A recent report6 described two patients with recurrent severe abdominal pain, nausea, and vomiting.6 The patients underwent three unnecessary laparotomies before the correct diagnosis was made.

The mainstay of therapy is discontinuation of the offending medication, which is usually sufficient in mild cases. More severe cases involving the tongue or causing respiratory compromise are treated with epinephrine, diphenhydramine, and steroids; however, no controlled studies have demonstrated the efficacy of these treatments.2 In cases of life-threatening respiratory compromise, an emergency cricothyroidotomy must be performed.2 Subsequent therapy should be initiated with an agent of an alternative class.

The prevalence of delayed angioedema will probably increase, given the growing number of patients on ACE inhibitors (35 to 40 million worldwide) and longer duration of therapy.2 Since 1995, I have seen six cases of late-onset angioedema among my clinic patients (five blacks, one white). Two of these patients were hospitalized.

All patients taking ACE inhibitors, particularly blacks, should be monitored for this potentially serious side effect. They should be informed that angioedema can occur even after many years of uneventful drug use. Patients should be advised to report mild and self-limited episodes and stop taking the ACE inhibitor immediately. On the other hand, physicians should consider the diagnosis of angioedema associated with the use of ACE inhibitors in every case of orofacial angioedema or otherwise unexplained acute or recurrent abdominal pain until it is definitely excluded by a thorough review of medications.

ADRIANA PAVLETIC, M.D., M.S.
Department of Family Medicine
University of Nebraska Medical Center
983075 Nebraska Medical Center
Omaha, NE 68198-3075

REFERENCES

1. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ. ACE inhibitor-induced angioedema. Incidence, prevention and management. Drug Saf 1998;18:171-88.
2. Agostoni A, Cicardi M. Drug-induced angioedema without urticaria. Drug Saf 2001;24:599-606.
3. Cohen EG, Soliman AM. Changing trends in angioedema. Ann Otol Rhinol Laryngol 2001;110: 701-6.
4. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. JAMA 1997;278:232-3.
5. Dean DE, Schultz DL, Powers RH. Asphyxia due to angiotensin converting enzyme (ACE) inhibitor mediated angioedema of the tongue during the treatment of hypertensive heart disease. J Forensic Sci 2001;46:1239-43.
6. Byrne TJ, Douglas DD, Landis ME, Heppell JP. Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? Mayo Clin Proc 2000;75:1201-4.

# Exhibit 09-83006

Aust N Z J Med. 1996 Dec;26(6):777-82.

Epidemiological study of angioedema and ACE inhibitors.

Gabb GM, Ryan P, Wing LM, Hutchinson KA.

Australian Medicines Handbook Pty Ltd, Adelaide, SA.

BACKGROUND: Angioedema is an uncommon and poorly recognised adverse reaction to angiotensin converting enzyme inhibitors (ACE-Is). The epidemiology of this association has not been described. AIMS: To examine the epidemiology of angioedema and its relation to ACE inhibitor prescribing. To examine the characteristics of angioedema occurring in patients taking ACE inhibitors. METHODS: A retrospective case control study and a case note audit were conducted of 40 patients who presented to a teaching hospital Accident and Emergency Department with angioedema on 48 occasions. One hundred and sixty control subjects presenting to the same Accident and Emergency Department but without angioedema were matched to cases by age, sex and presentation date. An ecological study comparing the numbers of angioedema admissions by age cohorts to South Australian (SA) public hospitals with the prescription volumes of ACE-Is in Australia was also undertaken. RESULTS: Case control study: In patients presenting with angioedema compared with controls, the exposure odds ratio for ACE-Is was 5.1 (95% CI 2.03-12.89) and for non-steroidal anti-inflammatory drugs (NSAIDs) was 4.13 (95% CI 1.28-13.39). CASE NOTE AUDIT: 15/40 (38%) patients presenting with angioedema on 19/48 (40%) occasions were taking an ACE-I. These patients were older and less likely to have an atopic history than those not taking an ACE-I. The onset of angioedema after starting an ACE-I was delayed for greater than six months in nine patients. ACE-I therapy was continued after 53% of presentations. ECOLOGICAL STUDY: The number of admissions with angioedema to SA public hospitals increased between 1985-86 and 1994-95, predominantly in older patients, and paralleled the increasing prescription volumes of ACE-Is. CONCLUSIONS: A considerable proportion of patients presenting with angioedema will be taking an ACE-I or a NSAID. The association of ACE-Is and angioedema is not well recognised, partly because the onset of angioedema may be delayed for months or years after commencement of an ACE-I. A persisting risk of angioedema is present in patients who have initially commenced an ACE-I uneventfully. The epidemiology of angioedema is now changing in parallel with the increasing use of ACE-Is.

# Exhibit 10-83006

Drug Saf. 1995 May;12(5):299-304.

Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers.

Lang DM.

Department of Medicine, Hahnemann University Hospital, Philadelphia, USA.

Studies have demonstrated greater hazards associated with anaphylaxis in patients receiving beta-blockers. Serious anaphylaxis is more frequent. Evidence suggests this occurs via modulation of adenylate cyclase, which can influence release of anaphylactogenic mediators. Treatment of anaphylaxis in patients exposed to beta-blockers is complicated because therapeutic administration of epinephrine (adrenaline) may be ineffective or promote undesired alpha-adrenergic and vagotonic effects. Risk reduction efforts should be considered for patients receiving beta-blockers who are prone to experience anaphylaxis.

# Exhibit 11-83006

CMAJ. 1987 May 1;136(9):929-33.

Beta-blocker therapy and the risk of anaphylaxis.

Toogood JH.

Beta-blocker therapy is associated with an increase in the severity and, possibly, the incidence of acute anaphylaxis. The population at risk consists of people with allergic conditions who are given a beta-blocker for an unrelated condition. Anaphylaxis under these conditions may be severe, protracted and resistant to conventional treatment because of the beta-adrenergic blockade. Severe or fatal attacks have been triggered by insect stings, the ingestion of allergenic foods or drugs, and injections of radiocontrast media, antisera or immunotherapy antigens. These occurrences are probably infrequent, but their incidence is unknown. At least two fatal cases have recently occurred in Canada. Clinical allergists, internists and family practitioners in particular should be aware of the need for aggressive and prolonged support in patients who experience anaphylaxis while receiving beta-blocker therapy and should report all such occurrences to the federal registry of adverse drug reactions. Allergy skin testing or immunotherapy is inadvisable in patients who take a beta-blocker orally or in the form of ophthalmic eyedrops. The list of relative contraindications to beta-blocker use should be extended to include susceptibility to recurrent anaphylaxis, whether it is idiopathic or due to an identifiable cause.

# Exhibit 12-83006

Cathet Cardiovasc Diagn. 1996 Dec;39(4):383-4

Refractory anaphylactoid shock potentiated by beta-blockers.

Javeed N, Javeed H, Javeed S, Moussa G, et al.

Jersey City Medical Center, New Jersey, USA.

Allergic reactions, including anaphylactoid shock due to contrast material, are not uncommon. However, persistent anaphylactoid shock refractory to conventional therapy is rare. We present a case of refractory anaphylactoid shock during coronary angiography unresponsive to aggressive standard therapy in a patient on beta-blockers. Significant clinical improvement was noted upon administration of glucagon. Since beta-blockers are commonly used in patients with coronary artery disease, this potentially life-threatening complication has to be kept in mind with any procedure involving contrast media in patients on beta-blockers. Immediate access to glucagon by keeping it in the procedure room may be lifesaving in these situations.